

Atypical Parkinsonism : Disentangling the Clinical Conundrum.

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Abstract : Objectives: To increase the awareness among clinicians by delineating the various syndromes under the umbrella of atypical Parkinsonism and to illustrate their varied clinical presentation, diagnosis, prognosis and treatment. **Methods:** Detailed web search was made in MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and CINAHL. **Results:** In stark contrast to idiopathic Parkinson's disease (PD) in which motor disability is the prime menace, nonmotor manifestations like cognitive and psychiatric dysfunction, autonomic disability, etc. are equally troubling for patients with atypical Parkinsonism. Progressive neurodegeneration invariably results in progression of both motor and nonmotor disabilities. Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) share several overlapping clinical features with idiopathic PD and the frontotemporal dementia syndromes and can be segregated by their differing neuropathology. Idiopathic PD is markedly responsive to Levodopa and other dopaminergic therapies for a long time in its course in comparison to the poor or no response in patients with atypical Parkinsonism. In fact, this widely different responsiveness to medication can be used to tilt the diagnosis to either side in borderline case scenarios faced by the clinicians concerned. As anticipated, deep brain stimulation (DBS) which is also highly dependent on Dopa responsiveness is ineffective in atypical Parkinsonism. Many newer treatment modalities are being tried, but the results are largely disappointing. More comprehensive knowledge regarding the fundamental neurological processes involved in both the motor and nonmotor domains of these disorders may help us to offer better therapy in the near future. A detailed understanding of neurophysiology of the basal ganglia and its complex circuitry with other centres in the neuraxis is of paramount importance to a clinician to fathom the varied clinical presentation and treatment responsiveness of these 'Parkinsonian Syndromes'. **Conclusion:** The term 'Atypical Parkinsonism' encompasses several entities which share many common clinical similarities with their 'typical' counterpart of idiopathic PD though the basic pathological processes differ. The importance of detailed history along with thorough clinical evaluation by eliciting specific clinical signs, pattern of disease onset, the course of the disease and responsiveness to medication, like in other subspecialties in neurology, cannot be overemphasized.

INTRODUCTION

Overall the parkinsonian syndromes may be 'typical' as in idiopathic Parkinson's disease (PD) or 'atypical' which include mainly Progressive supranuclear palsy (PSP), Multisystem atrophy (MSA), corticobasal degeneration (CBD), Vascular Parkinsonism (VaP), Dementia with Lewy bodies (DLB) and drug induced parkinsonism (DIP). Non motor manifestations may play a major role in the atypical group.¹ An alternative venture is to classify parkinsonism based on etiology which is illustrated in

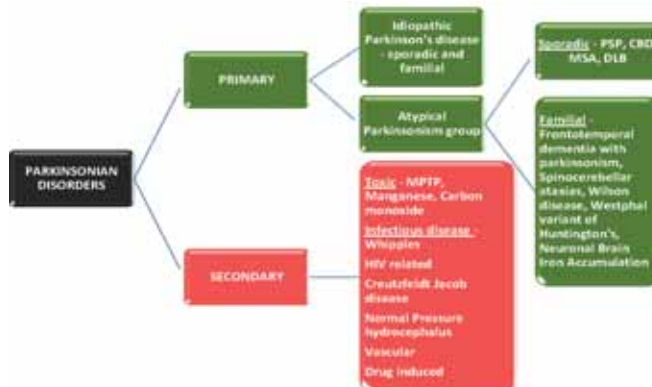


Figure 1: Etiological Classification of Parkinsonian Syndromes

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Figure 1.

The diagnosis of any parkinsonian syndrome is purely clinical since no single genetic, biochemical or radiological test can accurately rule in or out these disorders. Knowledge, awareness and experience of a clinician determines his diagnostic accuracy of a parkinsonian syndrome. However, newly emerging clinical signs in a patient may entirely change a previously established diagnosis. While differentiating idiopathic PD from the atypical forms have profound therapeutic implications, differentiating between the atypical parkinsonian disorders is also necessary for prognostication, planning for rehabilitation and reassurance in such patients. Various atypical features in a parkinsonian patient which divert the diagnosis away

Table 1: Red flags before diagnosing an idiopathic PD

Atypical motor features	Oculomotor	Autonomic	Cognitive
<ul style="list-style-type: none"> • Early falls • Rapid disease progression • Poor response to dopaminergic medications • Pyramidal signs • Ataxia • Early dystonia • Early dysphagia, dysarthria 	<ul style="list-style-type: none"> • Supranuclear gaze palsy • Oculomotor apraxia • Markedly slow saccades 	<ul style="list-style-type: none"> • Early orthostatic hypotension • Early impotence • Early bladder involvement • Prominent stridor 	<ul style="list-style-type: none"> • Early dementia • Apraxia • Higher cortical disturbances - neglect, visual hallucinations

from an idiopathic PD (Red Flags) are tabulated in Table 1.

Vague diagnoses like 'atypical parkinsonism', 'parkinson plus syndrome' or 'parkinsonian syndrome' offer little justice to these patients, caregivers or other medical personnel and hence the specific subtype of these disorders should be listed in a hierarchical manner as definitive differential diagnosis if no single diagnosis can be given confidently.

To label any patient as 'parkinsonian', the essential clinical feature to be elicited is bradykinesia. A reduction in speed and the amplitude of any movement is the hallmark of bradykinesia. The terms akinesia, hypokinesia and bradykinesia may seem similar but hold very different meanings and implications. Slowness in initiation of any movement indicates akinesia whereas both bradykinesia and hypokinesia deal with the way in which that movement is executed. Progressive decrement in speed or amplitude of repetitive movement is bradykinesia in contrast to slowed movement without a decrement in hypokinesia (Figure 2). Hypokinesia rather than bradykinesia may

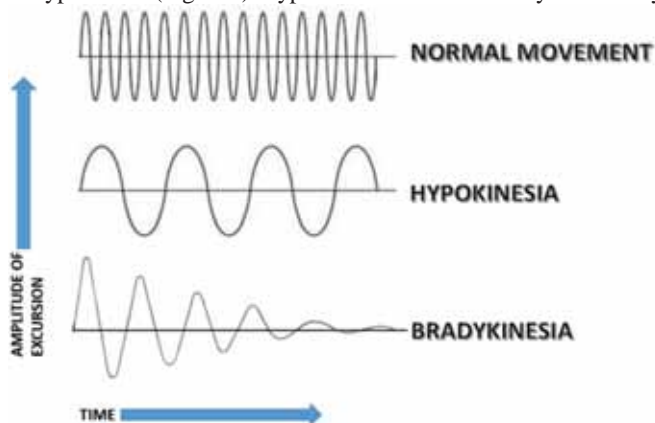


Figure 2: Hypokinesia Vs Bradykinesia

be the only sign of basal ganglia involvement in PSP.

Bradykinesia and hypokinesia may manifest during normal gait as a reduced arm swing with decreased stride length which may or may not progressively diminish (festination), during writing as micrographia, during vocalization as hypophonia, during swallowing as dysphagia, during facial expression as hypomimia, etc. Slowness of thought (Bradyphrenia) is a disabling nonmotor manifestation of these disorders and may be considered as the cognitive manifestation of slowness due to basal ganglia pathology. In the history, patients or family members may state that their daily activities like bathing take longer than usual and that they have become frailer gradually. Clinical testing of bradykinesia can be done with several methods. Repetitive finger tapping (index finger and thumb or all fingers with thumb), repetitive hand closure and opening, or repetitive foot or toe tapping against the floor. At least 15 seconds of observation may be necessary for any bradykinesia to manifest.² Due to bradykinesia and lack of associated movements, patients sit down, stand up or turn en bloc and usually fall 'like a tree' due to reduced reflex movements and sustain severe injuries to the hip, trunk or head in contrast to limb injuries due to attempted break of a fall in normal individuals. Bland facial expressions (hypomimia) may mimic depression, lack of motivation or interest and apathy.

Rigidity (lead pipe and cogwheel), resting tremors, postural instability and frequent falls, delayed or absent postural reflexes, stooped posture, motor blocks are the additional motor manifestations

common to these syndromes. In addition to basal ganglia, neurodegeneration involving other structures is implicated in the varied nonmotor manifestations like psychiatric, cognitive, autonomic, cerebellar and pyramidal dysfunction.

4 to 6 Hz resting tremors are classical of idiopathic PD albeit less pronounced in atypical syndromes. It is usually symmetrical if present in atypical forms in contrast to its asymmetry in idiopathic PD. Tremor usually disappears through the entire range of movement only to appear on reaching the target of interest (reemergent tremor). Mental concentration or distraction by the examiner can bring out such tremors which may not always be conspicuous. An observation of more than 60 seconds is necessary before ruling out resting tremors. Reemergent tremors usually appear in 5 to 10 seconds of assuming a new posture. Tremors of the lower limbs while standing and resting tremors of the lower jaw can also be present.

Rigidity may present as pain or 'stiffness' of joints or limbs as the major complaint. Elderly individuals presenting to neurology OPD with arthralgia, myalgia, lumbago or periartthritis shoulder should be checked for an underlying rigidity as the culprit. Passive movement of the wrist, forearm, elbows, knees, ankles or head usually reveals rigidity which can be axial, appendicular or a combination. Activated rigidity (Froment sign) is brought out by asking the patient to actively perform repetitive actions in the contralateral limb (like opening and closing the hand) while passively testing for rigidity in the ipsilateral limb. Unusually increased resistance to passive motion may be velocity dependent (spasticity – clasp knife) or velocity independent (rigidity – lead pipe, cogwheel with superimposed tremors).

PSP or MSA present predominantly with gait instability which is a feature only in advanced cases of idiopathic PD. Difficulty in negotiating uneven ground, frequent falls and inability to multitask while walking (due to defective autopilot) like talking on the phone may all be the manifestations of a gait disturbance. At least a 10 meter walk may need to be observed before ruling out gait disturbance. Fluidity of patients' movements while turning or negotiating through obstacles or uneven ground may give more clues than routine walking. Gait freezing usually manifests before a change in speed or direction of walking. Narrow based gait with short stride length and reduced arm swing are classical. Patients with MSA or PSP show an impaired tandem gait.³ Frank ataxic gait may also occur in advanced cases of these diseases. A lurching gait with an increased tendency to fall indicates PSP.

i) Progressive supranuclear palsy:

PSP, a neurodegenerative tauopathy must always be in the back of a physician's mind when dealing with a patient presenting with parkinsonism but lacking responsiveness to levodopa. Marked postural instability with frequent falls at presentation, conspicuous executive dysfunction, supranuclear vertical gaze palsy and dysarthria or dysphagia tattle PSP as the culprit in a parkinsonian patient. PSP can further be dissected into various subtypes like the classic form of Steele Richardson Olszewski syndrome, PSP-parkinsonism (PSP-P), PSP-pure akinesia with gait freezing, PSP-corticobasal syndrome (PSP-CBS), and PSP – frontotemporal dementia (PSP-FTD). The Clinical Criteria for the Diagnosis of Progressive Supranuclear Palsy by National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) is illustrated in Table 2.⁴

a) Steele Richardson Olszewski syndrome

Patients with classical Richardson syndrome present with early gait

instability and personality changes. The age of onset is typically later than a case of an idiopathic PD. Apathy is often noticed by the relatives in close contact with the patient. Slowing of vertical saccades gradually worsens to frank supranuclear gaze palsy. Hypometric saccades, fixation instability causing square wave jerks are additional oculomotor manifestations.⁵The severity of these eye movement anomalies usually correlate with midbrain atrophy in imaging. In advanced stages the eyes may completely become fixed in all planes. Apraxia and dystonia which are more characteristic of CBS may also present occasionally with PSP. Executive dysfunction due to impaired processing speed is also common. Retropulsion or the pull test is usually sufficient to identify the marked postural instability in Richardson syndrome which is out of proportion to bradykinesia. Autonomic dysfunction, ataxia are less common. The usual course of disease from onset to dependence on others for daily activities is around 4 years and to death is 7 years.⁶Severe dysarthria resulting in unintelligible speech, marked cognitive slowing, impaired swallowing

Table 2: NINDS – SPSP criteria for the diagnosis of Progressive supranuclear palsy

INCLUSION CRITERIA
<ul style="list-style-type: none"> • Possible - Gradually progressive disorder with age of onset 40 or more with either vertical supranuclear gaze palsy or both slowing of vertical saccades and prominent postural instability (with tendency to fall) in first year of disease onset • Probable - Gradually progressive disorder with age of onset 40 or more with vertical supranuclear gaze palsy and prominent postural instability (with tendency to fall) in first year of disease onset • Clinically possible or probable PSP with histopathological evidence of PSP
EXCLUSION CRITERIA
<ul style="list-style-type: none"> • Recent history of encephalitis • Alien limb syndrome • Cortical sensory deficits • Focal frontal or temporoparietal atrophy • Hallucinations or delusions unrelated to dopaminergic therapy • Cortical dementia of Alzheimer type • Prominent, early cerebellar symptoms • Unexplained dysautonomia • Neuroradiological evidence of relevant structural abnormality
SUPPORTIVE CRITERIA
<ul style="list-style-type: none"> • Symmetrical akinesia or rigidity, proximal more than distal • Abnormal neck posture, especially retrocollis • Poor or absent response of parkinsonism to levodopa • Early dysphagia and dysarthria • Early onset of cognitive impairment including two or more of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs

causing frequent aspirations and pneumonia occur in the pre-terminal stage.⁷

b) PSP – Parkinsonism

Bradykinesia and rigidity (predominantly axial) are more marked in this subgroup which may or may not be symmetric and can be associated with a resting tremor. Kinetic tremors may also occur.⁸ In contrast to other subtypes, good initial response to dopaminergic medications may be seen which may prompt many to brand these patients as idiopathic PD. In fact, it may be impossible to differentiate between these two at the onset. Rapid progression, predominant axial rigidity, dopaminergic unresponsiveness occurring a lot earlier are some of the clues which tilt the diagnosis towards PSP-P.⁹Progression of the disease over years may also blur the difference between a case

of PSP-P and the classical Richardson type since both the groups develop cognitive decline, postural instability and gaze palsies though patients with PSP-P live relatively longer.¹⁰

c) Pure akinesia with gait freezing

This type is less frequent. As the name implies, these patients present with isolated difficulty in initiation of movements with frequent freezing.¹¹Gait initiation failure is gradually accompanied by gait instability and falls, axial rigidity, vertical gaze paresis, hypophonia and hypomimia. Onset to death duration usually surpasses 10 years.^{12,13}Prominent early cognitive slowing is unusual and prompts a change in diagnosis.

d) PSP-corticobasal syndrome

The manifestations of corticobasal syndrome which typically occurs with corticobasal degeneration may also occur in PSP and it may be impossible to distinguish between these two. Ideomotor apraxia, parkinsonism unresponsive to dopaminergic medication, aphasia, cortical sensory loss, dystonia and myoclonus are the clinical features.

e) PSP-frontotemporal dementia

Behavioural variant of FTD and progressive nonfluent aphasia may present later (usually after 5 years from diagnosis) with PSP like features like gaze palsy, postural instability, bradykinesia and axial rigidity.^{14, 15}

Substantial midbrain atrophy results in the characteristic ‘humming bird sign’ or ‘penguin’ in MRI (Figure 3). Midbrain atrophy also manifests as increased concavity of lateral walls of the midbrain tegmentum giving rise to characteristic ‘Morning glory’ appearance



Figure 3: Humming Bird Sign In T2 SAGITTAL MRI (Arrow) - A Manifestation Of Midbrain Atrophy In PSP

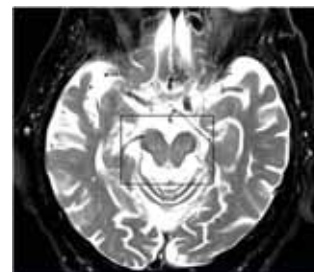


Figure 4: Morning Glory Sign In T2 Axial MRI – Due To Increased Concavity Of The Lateral Margins Of Midbrain Tegmentum - Another Manifestation Of Midbrain Atrophy In PSP

in axial MR images (Figure 4). Magnetic resonance parkinsonism index which is calculated by the formula (midsagittal pons area*width of middle cerebellar peduncle)/ (midbrain area*width of superior cerebellar peduncle) with value more than 13.55 indicates PSP.¹⁶

Pallidum, substantia nigra pars compacta and reticularis, oculomotor, vestibular and dentate nuclei, superior colliculi, frontal cortices and periaqueductal grey are all involved in PSP. Globose tau positive neurofibrillary tangle mark this disorder histopathologically.

Main treatment is symptomatic and palliative. Patient education,

support and counselling are crucial. Patients need to be informed about the inevitable worsening and the need for prior arrangements in such situations of increasing dependence. Trial of different dopaminergic medications is warranted in almost all situations. In addition psychiatric comorbidities like depression and anxiety, sleep disturbances and joint or muscle pains need to be appropriately addressed. Physiotherapy, occupational therapy and speech therapy as in all other neurodegenerative disorders are equally important. Severe dysphagia may require gastrostomy tube feeding. PSP-P may respond well to dopaminergics initially though the efficacy may be lost within months of institution. In all cases Levodopa responsiveness needs to be tested with gradually increasing doses up to 1200 mg/day over a month. Dopamine agonists are not usually helpful. Amantadine may alleviate freezing and sialorrhea. Bladder care and catheterization when necessary alleviates patient's distress.

i) Multiple system atrophy

Cardiologist, gastroenterologist, urologist may all have been consulted before a neurologist's opinion is sought as a last resort in patients with MSA. Progressive autonomic dysfunction which predates motor symptoms by several years may easily impersonate non neurological disorders. Striatonigral degeneration, Olivopontocerebellar atrophy and isolated autonomic failure are all within the realms of MSA. Patients present with urinary difficulties, constipation, orthostatic hypotension, erectile dysfunction, etc. and later develop parkinsonism which is usually symmetrical. Selective degeneration of the pontocerebellar tracts result in characteristic T2 hyperintensities which form a cross ('hot cross bun sign') on axial MR images through the pons (Figure 5). This sign is nonspecific and may be seen in spinocerebellar atrophy type 2 and 3, variant Creutzfeldt-Jakob disease and parkinsonism secondary to vasculitis.¹⁷ Other neuroimaging features include a slit like signal abnormality in

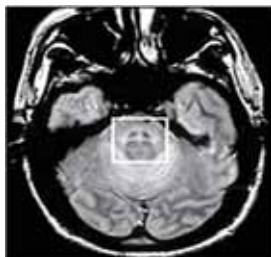


Figure 5 – T2 Axial MRI Showing Hot Cross Bun Sign – A Manifestation Of Pontocerebellar Tract Atrophy In MSA

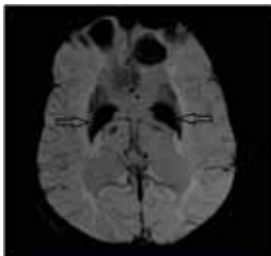


Figure 6 – Excess iron deposition in pallidum and putamen in susceptibility weighted MRI (arrows) – A finding in MSA



Figure 7 – T1 AXIAL MRI showing characteristic pontine atrophy in MSA (Solid White Arrow). Compare to the relatively preserved size of the midbrain above.

the posterolateral putamen due to atrophy or excessive iron deposition (Figure 6). Pontine atrophy may be pronounced in axial MRI (Figure 7). Patients may present with predominant parkinsonian (MSA-P) or cerebellar (MSA-C) dysfunction. The proposed diagnostic criteria for diagnosis of MSA is depicted in Table 3.¹⁸

Table 3: Diagnostic criteria for MSA

CRITERIA FOR POSSIBLE MSA

- A sporadic, progressive, adult (>30 y)–onset disease characterized by
- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and
- At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and
- At least one of the additional features - Babinski sign with hyperreflexia or stridor (for possible MSA-P or MSA-C), Rapidly progressive parkinsonism, poor response to levodopa, postural instability within 3 y of motor onset, gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction, dysphagia within 5 y of motor onset, atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum, hypometabolism on FDG-PET in putamen, brainstem, or cerebellum (for possible MSA-P) and parkinsonism (bradykinesia and rigidity), atrophy on MRI of putamen, middle cerebellar peduncle, or pons, hypometabolism on FDG-PET in putamen, presynaptic nigrostriatal dopaminergic denervation on SPECT or PET (for possible MSA-C)

CRITERIA FOR PROBABLE MSA

- Sporadic, progressive, adult (>30 y)–onset disease with
- Sporadic, progressive, adult (>30 y)–onset disease with
- Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males)
- Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and
- Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

CRITERIA FOR DEFINITE MSA

- Neuropathologic evidence of CNS alpha-synuclein–positive glial cytoplasmic inclusions with neurodegenerative changes in striatonigral or olivopontocerebellar structures

Postural instability and falls occur within 3 years of disease onset. Stimulus sensitive myoclonus is frequent. Postural BP recordings reveal orthostatic hypotension. A fall in systolic pressure by more than 20 mm Hg and diastolic pressure by more than 10 mm Hg after 3 minutes of standing from lying position without an increase in pulse rate indicates autonomic dysfunction. Poor prognostic factors are early autonomic failure, early falls, cognitive impairment, severe dysphagia, and wheelchair dependence.

Hyperreflexia can be found across all the parkinsonian syndromes but a positive Babinski is seen only in MSA and not in idiopathic PD. MSA patients may adopt an extreme flexed posture which is unusual in idiopathic PD. Argyrophilic neuronal and glial cytoplasmic inclusions which contain alpha synuclein are pathognomonic but may occasionally be seen in PSP or CBD.

Dopaminergic medications are useful in a third of MSA-P patients, though they can exacerbate orthostatic hypotension. Their efficacy is less pronounced and short lasting compared to idiopathic PD. Autonomic dysfunction needs to be countered with fludrocortisone

and midodrine, indomethacin or pyridostigmine (which increase vascular resistance) in severe cases. Increased salt intake and compression stockings are other alleviatory measures. Bladder spasticity responds to peripherally acting anticholinergic medications or local botulinum toxin. Supportive and palliative care are similar to those described for PSP.

i) Corticobasal degeneration

Varied presentations of CBD make it a very challenging disorder to diagnose. Definitive diagnosis may in many cases be reached only during an autopsy. Corticobasal syndrome classically is a feature of CBD, although similar presentations of PSP, FTD or Alzheimer disease is also feasible. Asymmetric progressive ideomotor apraxia is the classical presentation frequently affecting the hand associated with rigidity, myoclonus and dystonia, gradually involving all four extremities with persistent asymmetry. Apraxia and rigidity are more frequent and more pronounced than the other symptoms. Alien limb

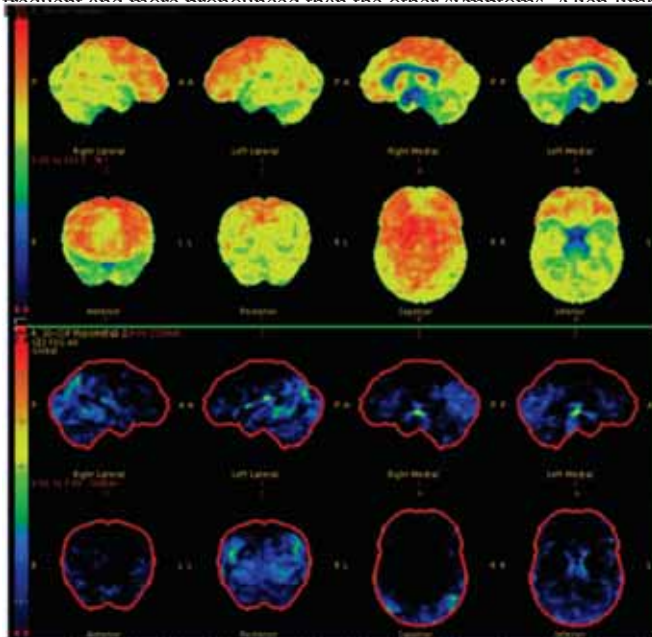


Figure 8: Asymmetric Posterior Frontal And Inferior Parietal Hypometabolism In PET Imaging Suggestive Of CBD

Table 4 is the recently proposed diagnostic criteria for a diagnosis of a corticobasal syndrome.¹⁹

Table 4: Diagnostic criteria for Corticobasal degeneration

Probable CBS

Asymmetric onset with

- ➔ **Two out of three**
- Limb rigidity or akinesia
 - Limb dystonia
 - Limb myoclonus

- ➔ **Plus two out of three**
- Orobuccal or limb apraxia
 - Cortical sensory loss
 - Alien limb phenomenon

Possible CBS

Asymmetric onset with

- ➔ **One out of three**
- Limb rigidity or akinesia
 - Limb dystonia
 - Limb myoclonus

- ➔ **Plus one out of three**
- Orobuccal or limb apraxia
 - Cortical sensory loss
 - Alien limb phenomenon

Swollen, tau positive, achromatic neurones – Pick cells are the characteristic histopathological findings. Asymmetric parietal or frontoparietooccipital atrophy is present in imaging. CBD-PSP is differentiated from classical Richardson type by a relatively more severe cognitive and behavioural disturbances (disinhibition) in the former in borderline cases. Survival in CBD is around 7 to 8 years since diagnosis. Dopaminergic medications should be tried although they are ineffective in majority of cases. Myoclonus must be treated with valproate, clonazepam or levetiracetam and botulinum toxins may be tried for troubling dystonia. Supportive and palliative care are similar to the other subtypes.

i) Vascular Parkinsonism

There is debate regarding whether VaP is a distinct entity or is just a mixture of pathologies. VaP usually presents with a lower body predominant parkinsonism with imaging revealing extensive subcortical white matter lesions.²⁰ Pyramidal signs are predominant in half of these cases which strongly differentiates this subtype from an idiopathic PD. Stepwise progression with lesions involving globus pallidus, substantia nigra, ventrolateral nucleus of the thalamus and frontal cortex are common. Absence of characteristic subcortical lesions makes differentiation from the other subtypes difficult.

ii) Dementia with Lewy bodies

It is a progressive degenerative dementia with visual hallucinations and fluctuating behaviour preceding the motor signs. In contrast to Alzheimer's disease extrapyramidal features present earlier and are more severe. Executive function deficits and visuospatial dysfunction are the other prominent cognitive impairments. Syncope related to orthostatic hypotension, delusions and exquisite neurolept sensitivity are other pointers towards DLB. During formal mental status assessment, patients alternate between being alert, oriented and coherent and becoming confused and less responsive to testing despite appearing fully awake. This is characteristic of DLB. REM sleep behaviour disorders and myoclonus may occur. Positron emission tomography (PET) imaging reveals decreased occipital blood flow in DLB (Figure 9). Abnormal dopamine transporter (DAT) scans have a sensitivity of 75% and specificity of 90% for DLB.²¹ PET imaging with Pittsburgh compound B show amyloid deposits similar to that of Alzheimer's disease.

Histopathology reveals the characteristic lesion – Lewy body, which is an eosinophilic inclusion body in the cytoplasm of substantia nigra, locus ceruleus, nucleus basalis of Meynert, dorsal raphe and dorsal motor nucleus of Vagus. Nonpyramidal cells in layers 5 and 6 of the cortex may harbour Lewy bodies.

Rivastigmine is shown to reduce psychiatric symptoms like apathy, hallucinations and delusions in DLB.²² Donepezil and galantamine may also be effective. Neuroleptics like haloperidol are contraindicated while atypical neuroleptics like quetiapine and clozapine may be used with caution. Memantine may be tried for improving cognition. Dopaminergic trial is indicated for parkinsonian symptoms with a risk of exacerbating psychosis and confusion. Depression usually responds to selective serotonin reuptake inhibitors (SSRIs). REM sleep behaviour disorders respond to clonazepam.

iii) Drug induced Parkinsonism

Older age, female gender (estrogen possibly suppresses the dopamine receptor expression), and genetic factors are all risk factors for developing DIP.^{23, 24} Common drugs that are implicated in DIP are tabulated in table 5.

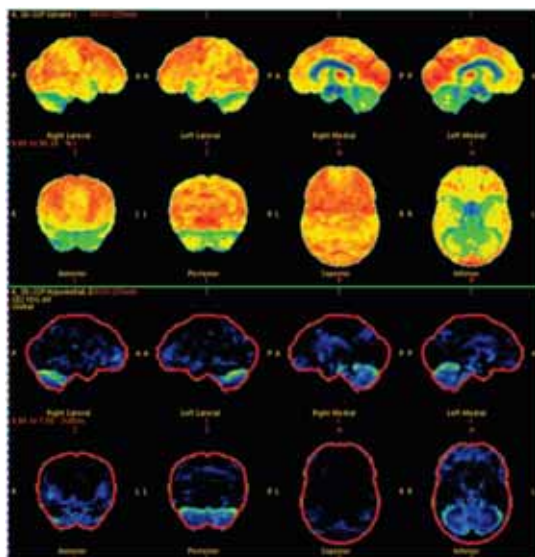


Figure 9: DIFFUSE Symmetric Hypometabolism In Bilateral Occipital Lobes, Parietal Lobes And Medial Frontal Lobes In PET Imaging Suggestive Of DLB.

DIP is generally a bilateral and symmetric parkinsonism with marked rigidity and bradykinesia. Resting tremors and postural tremors may also occur. It has been suggested that many such patients may have had an underlying preclinical or subclinical PD only to be unmasked by these drugs. The parkinsonian features may not resolve completely in all patients and may persist or even progress in some cases, supporting the notion that DIP may in fact be just a precipitation of an underlying idiopathic PD. In such cases, dopaminergic therapy may be fruitful.²⁵DAT imaging may be used for patients with DIP to uncover an underlying idiopathic PD.

Dopamine receptors in the brain belong to two groups – the D1 family (D1 and D5 receptors) and the D2 family (D2-4 receptors). All antipsychotics are potent D2 blockers which in turn disinhibits GABAergic and encephalineric striatal neurons of the indirect pathway leaving the direct pathway intact. This leads to inhibition of the thalamocortical projections through globus pallidus and substantia nigra pars reticulata causing bradykinesia and rigidity. Long term T2 receptor blocking may result in D2 supersensitivity which is implicated in Tardive dyskinesia.

i) Investigation in Atypical Parkinsonism

Standard blood investigations are normal. Anal and sphincter EMG may show polyphasic potentials in MSA portraying the underlying degeneration of the Onuf nucleus. Structural and functional neuroimaging are often necessary for a diagnosis. A number of mimics like basal ganglia calcifications, infarcts, haemorrhage or mass lesions, hydrocephalus, demyelination, cerebellar tumors, infarcts or haemorrhage, etc. can be ruled out with structural MR imaging. Classical structural and functional imaging features of the various parkinsonian syndromes are highlighted in table 6.

CONCLUSION

To sum up, thorough and focussed history and vigilant clinical examination along with investigations can identify atypical parkinsonism in majority of the cases. A succinct illustration of the various clinical cues in the parkinsonian syndromes is presented in table 7.

Table 5: Common drugs implicated in DIP

DRUGS MORE LIKELY TO CAUSE DIP	DRUGS LESS LIKELY TO CAUSE DIP
TYPICAL ANTIPSYCHOTICS:	ATYPICAL ANTIPSYCHOTICS: clozapine, quetiapine
Phenothiazines: chlorpromazine, prochlorperazine, perphenazine, promethazine, fluphenazine,	MOOD STABILIZERS: lithium
Diphenylbutylpiperidines: pimozide	ANTIDEPRESSANTS: SSRIs (fluoxetine, citalopram, sertraline)
Benzamide substitutes: sulpiride	ANTIPILEPTICS: phenytoin, valproate
Butyrophenones: haloperidol	ANTIEMETICS: domperidone, etopride
ATYPICAL ANTIPSYCHOTICS: risperidone, olanzapine,	
ziprasidone, aripiprazole	
DOPAMINE DEPLETERS: tetrabenazine, reserpine	
CALCIUM CHANNEL BLOCKERS: cinnarizine, flunarizine	
ANTIEMETICS: metoclopramide	

Table 6: Imaging in Atypical Parkinsonism

DISEASE	STRUCTURAL IMAGING	FUNCTIONAL IMAGING
Idiopathic PD	Heterogeneous nigral signal loss	Asymmetrical striatal low uptake of F-dopa, FPCIT, beta CIT Normal putamen FDG Normal HMRS NAA Cr ratio
PSP	Midbrain atrophy and consequent dilatation of the third ventricle resulting in 'humming bird' sign or 'penguin' sign Increased MR parkinsonism index (>13.55) - Refer text	Symmetrical striatal low uptake of F-dopa, FPCIT, beta CIT Symmetric low putamen and caudate FDG Low HMRS NAA Cr ratio Low frontal FDG
MSA	Hot cross bun sign in axial sections of pons due to pontocerebellar tract atrophy Cerebellar atrophy, Pontine atrophy Slit like posterior putamen signal anomaly due to iron deposition	Asymmetrical striatal low uptake of F-dopa, FPCIT, beta CIT Asymmetric low putamen FDG Low HMRS NAA Cr ratio
CBD	Asymmetrical cortical atrophy	Low cerebellar FDG Asymmetrical striatal low uptake of F-dopa, FPCIT, beta CIT Asymmetric low putamen and caudate FDG Low HMRS NAA Cr ratio Asymmetric low thalamic, posterior frontal and inferior parietal FDG

Abbreviations: F-dopa - Fluoro dopa; FPCIT – Fluoropropyl Iodine-123-beta-carbomethoxy-3 beta-(4-iodophenyl)tropane; CIT - Iodine-123-beta-carbomethoxy-3 beta-(4 iodophenyl)tropane, FDG – Fludeoxyglucose, HMRS – Hydrogen magnetic resonance spectroscopy, NAA Cr ratio – N acetyl aspartate to creatine ratio

Table 7: Important clinical clues in Parkinsonian syndromes.

CLINICAL FEATURE	IDIOPATHIC PD	PSP	MSA	CBD
RIGIDITY	Usually asymmetrical Limb predominant	Symmetrical axial predominant	Usually asymmetrical Limb predominant	Usually asymmetrical Limb predominant
BRADY/HYPOKINESIA	Bradykinesia	Hypokinesia > Bradykinesia	Bradykinesia	Apraxia > Brady/hypokinesia
TREMOR	Asymmetrical 4-6 Hz, extremities, jaw	Unusual	Asymmetrical 4-6 Hz, extremities	Asymmetrical, stimulus sensitive myoclonus may occur
FACIAL EXPRESSION	Hypomimia with reduced blink rate	Staring look, eyelid apraxia	Hypomimia, facial dyskinesias	Hypomimia, orobuccofacial apraxia
GAIT AND STATION	Normal in early stage, late falls, festination	Early falls, retrocollis	Early falls, flexed posture, pronounced anterocollis	Early falls may occur
OCULAR MOVEMENTS	Hypometric saccades	Supranuclear gaze palsy, fixed eye - late stages	Hypometric saccades, nystagmus	Supranuclear gaze palsy may occur
LOWER CRANIAL NERVE	Late dysarthria, dysphagia, hypophonia	Early dysarthria, dysphagia	Early stridor, dysarthria, dysphagia	Early dysarthria, dysphagia
ATAXIA	Absent	Unusual	Usual	Unusual
APRAXIA	Absent	Eye lid apraxia	Unusual	Usual
AUTONOMIC DYSFUNCTION	Early impotence, late orthostatic hypotension	Early impotence, rarely late orthostatic hypotension	Early Orthostatic hypotension, bladder, constipation and impotence	Early impotence, rarely late orthostatic hypotension
ALIEN PHENOMENON	Limb Absent	Absent	Absent	Unusual